REVIEW

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Cross talk between natural killer cells and mast cells in tumor angiogenesis

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Abstract

Natural killer (NK) cells are large granular lymphocytes of the innate immune system, responsible for direct targeting and killing of both virally infected and transformed cells. Under pathological conditions and during inflammation, NK cells extravasate into the lymph nodes and accumulate at inflammatory or tumor sites. The activation of NK cells depends on an intricate balance between activating and inhibitory signals that determines if a target will be susceptible to NK-mediated lysis. Many experimental evidences indicate that NK cells are also involved in several immunoregulatory processes and have the ability to modulate the adaptive immune responses. Many other important aspects about NK cell biology are emerging in these last years. The aim of this review is to elucidate the role of NK cells in tumor angiogenesis and their interaction with mast cells. In fact, it has been observed that NK cells produce pro-angiogenic factors and participate alone or in cooperation with mast cells to the regulation of angiogenesis in both physiological and pathological conditions including tumors.

Keywords Angiogenesis · Anti-angiogenesis · Mast cells · NK cells · Tumor growth

NK cell distribution in healthy tissues

Natural killer (NK) cells originate from hematopoietic stem cells (HSC) and undergo maturation primarily in the bone marrow, where stromal cells produce factors sustaining proliferation and differentiation of NK progenitors [1]. Immature NK cells are CD16$^-$ and CD56$^-$, but express CD161 and exert cytolytic functions [2]. During differentiation process, the expression of CD34 is progressively lost, while other surface antigens specific for the NK lineage appear. In addition, NK cells progressively acquire the expression of inhibitory and activating receptors as well as their functions of cytokine secretion and cytotoxicity [3]. NK cells account for 5–15% of the peripheral blood lymphocytes and exert cytotoxic functions [4]. More than 90% of NK cells are found in the blood circulation, where they express high amounts of CD16 and low amounts of CD56 (or NCAM, neural cell adhesion molecule), while other NK cells express high amounts of CD56, lack of CD16, and have low cytotoxic activity [5]. Less than 10% of NK cells are found in healthy tissues, such as skin, gut, spleen, liver, lungs, and uterus during pregnancy. Uterine NK cells are predominantly CD56$^{+\text{Bright}}$, whereas this subset represents only 10% of the peripheral blood population, and the relationship between peripheral and uterine NK cells is unclear [5]. In comparison to humans, two functionally disparate populations of uterine NK cells have been identified in mice, which are distinguished by their reactivity to *Dolichos biflorus agglutinin* (DBA). The roles of uterine NK in both human and mouse are the production of cytokines, chemokines and angiogenic factors, which may mediate the physiological processes required for successful pregnancy [5].

Most NK cells have large granular lymphocytes (LGLs) morphological aspects [6]. LGLs constitute 2–6% of the peripheral white cells and approximately 10–15% of peripheral blood lymphocytes. LGLs are larger than the typical lymphocytes (10–12 μm) with a large amount of cytoplasm containing peroxidase-negative granules. However, not all NK cells have LGL morphology and not all LGL cells are NK cells. Human LGLs contain primary lysosomes

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characterized by an electron dense core surrounded by a layer of lesser opacity. In addition to lysosomal enzymes, the granules contain phospholipids, proteoglycans, and proteins important for cytotoxic lymphocyte functions, including serine esterase (granenzymes) and performing proteins (perforins) [7]. The combined functions of these proteins lead to the generation of pores on the plasma membrane and activation of the caspase cascade. The majority of NK cells found in reactive lymph nodes and peripheral tissues are poor cytolytic (perforin low), while in the peripheral blood most NK cells are high cytolytic (perforin high) [8].

NK cells in pathological conditions

Under pathological conditions and during inflammation, NK cells extravasate into the lymph nodes and accumulate at sites of tumor growth. Mice with compromised NK cell function are more susceptible to carcinogen-induced cancers, and individuals lacking NK cells suffer from persistent viral infections and as a consequence die prematurely. NK cells exert cytotoxic functions mainly directed against virus-infected cells and tumor cells [4]. They also display immunomodulatory functions through secretion of immunoregulatory cytokines, such as interferon-gamma (IFN-γ,) tumor necrosis factor-alpha (TNF-α), interleukin-10 and − 13 (IL-10, IL-13), and granulocyte colony stimulating factor (GM-CSF), but they have a low natural cytotoxicity [9]. NK cells acts in an activating and inhibiting way by expressing different receptors [10].

The activation of NK cells depends on an intricate balance between activating and inhibitory signals that determines if a target will be susceptible to NK-mediated lysis. To "see" and discriminate between normal and transformed cells, NK cells express activating and inhibitory membrane receptors that recognize ligands at the surface of target cells. NK cells spontaneously lyse tumor targets in vivo and in vitro without requiring immunization or pre-activation. Cytokines including IFN-α/-β, IL-2, IL-12 and IL-15 enhance NK cell-mediated cytotoxicity, whereas IL-2 and IL-12 induce NK proliferation, and IL-1, IL-2, IL-12, IL-15, IL-18 and TNF induce NK lymphokine production. NK cells provide surveillance against tumor cells and virus-infected cells [11]. In experimental in vivo models, NK cells can destroy tumor cells, and are effective in eliminating tumor cells and prevent metastasis [12]. Higher incidence of lymphoproliferative disorders have been demonstrated in patients with Chediak–Higashi syndrome, which have profound deficits in NK activity, and in patients with X-linked lymphoproliferative diseases, NK activity is deficient as well [13]. NK cells often are decreased in pathological conditions, including cancer and AIDS [4].

Angiogenic factors secreted by NK cells

NK cells secrete pro-angiogenic cytokines, including vascular endothelial growth factor (VEGF), placental growth factor (PlGF), IL-8, IL-10, transforming growth factor beta (TGF-β), angiopoietin (Ang)-1 and Ang-2 [14–16]. VEGF seems to be the most relevant. In fact, loss of hypoxia inducible factor-1 alpha (HIF-1α) in NK cells increased the bioavailability of VEGF by decreasing the infiltration of NK cells that express angiostatic soluble VEGF receptor-1 (VEGFR-1) [17]. Moreover, NK cell depletion leads to reduction of corneal angiogenesis associated with reduced macrophage infiltration and lower levels of VEGF-A [18], and zoledronic acid synergize with IL-2 in inducing pro-angiogenic activity of NK cells acting on VEGF [19].

NK and angiogenesis in female reproductive system

Angiogenesis is an essential process for proper functioning of the female reproductive system and for successful pregnancy realization. Even though immune cells are differentially distributed in each organ of the reproductive tract, the predominant immune cells are T cells, macrophages/dendritic cells, NK cells, neutrophils, and mast cells. The major phenotype of endometrial NK cells is CD3−CD56brightCD16−, which distinguishes this cell subset from CD3−CD56dimCD16+ NK cells in the peripheral blood [20]. NK cells represent more than 70% of the lymphocytes in human decidual cell suspensions and up to 30% of the cells found histologically in the mesometrial regions of murine implantation sites.

In mice, NK cells are essential for the initiation of pregnancy-associated spiral arterial modification through their production of IFN-γ and VEGF. VEGF provides not only a potent pro-angiogenic stimulus but works as an important stem cell survival factor with ability to recruit cells into the hypoxic environments [21]. Thus, it might act as endothelial tip cell guidance towards hypoxic endometrium not only in the endometrial/decidual environment occupied by the trophoblasts but also in the necrotic milieu that occurs during endometrial destruction in the menstrual cycle. Moreover, uterine NK cells contribute to the physiological vascular remodeling in the uterus during the secretory phase of menstrual cycle as well as during pregnancy [22]. In the decidua, NK cells are closely linked to its vascularization and spiral artery formation [23]. Decidual NK cells synthesize angiogenic factors, including VEGF, PlGF, and IL-8 and show angiogenic activity

both in vitro and in vivo [14]. NK cells are the most abundant leukocytes in preimplantation endometrium, accumulate and actively proliferate in the endometrium of murine, porcine and human developing placenta [24].

NK and angiogenesis in tumors

A pro-tumorigenic phenotype of cancer infiltrating NK cells has been demonstrated due to their ability to release angiogenic factors and immunosuppressive cytokines [25]. In non-small cell lung cancer (NSCLC), NK cells synthesize higher VEGF, IL-8 and PlGF as compared to controls [26]. Moreover, supernatants derived from NSCLC cells induce endothelial cell chemotaxis and formation of capillary-like structures in vitro [26]. More recently, Bruno et al. [27] have demonstrated the expression of angiogenin, matrix metalloproteinase-2 (MMP-2), and tissue inhibitor of MMP (TIMP) by NK cells in patients with colorectal cancer. Moreover, STAT3/STAT5 activation was observed in tumor NK cells, and treatment with pimozide, a STAT5 inhibitor, reduced angiogenic capability of endothelial cells, inhibiting VEGF production [27].

NK cells are required mediators of angiogenesis inhibition by IL-12 in an IFN-γ-dependent manner, and NK cell cytotoxicity of endothelial cells is a potential mechanism by which IL-12 can suppress neovascularization [28]. IL-12 receptors indeed are present primarily on NK cells and T cells [29]. IL-12-activated lymphocytes influence inhibition of tumor growth and function as an anti-vascular agent, by releasing higher level of IFN-γ and down-modulating VEGF [30]. The genetic inactivation of STAT-5, which is required for NK cell-mediated immunosurveillance, upregulates VEGF-A in NK cells, enhances angiogenesis in a mouse lymphoma models and on healthy donor-derived NK cells [31].

Mast cells and angiogenesis

Mast cells (MCs) produce several pro-angiogenic factors, including fibroblast growth factor-2 (FGF-2), VEGF, IL-8, TNF-α, TGF-β, and nerve growth factor (NGF) [32]. Mast cells migrate in vivo and in vitro in response to FGF-2, VEGF and PlGF-1 [33]. Human lung mast cells express VEGF-A, and induce angiogenic response in the chick embryo chorioallantoic membrane (CAM) assay that was inhibited by an anti-VEGF-A antibody [34]. Granulated murine mast cells and their granules are able to stimulate an intense angiogenic reaction in the CAM assay, inhibited by anti-FGF-2 and -VEGF antibodies [35]. Among the angiogenic factors stored in mast cell granules it is to note the role played by two proteases, i.e., chymase and tryptase.

Tryptase added to microvascular endothelial cells cultured on Matrigel caused a pronounced increase in capillary growth, suppressed by specific tryptase inhibitors. Moreover, tryptase directly induced endothelial cell proliferation in a dose-dependent fashion. Chymase induces angiogenesis by converting angiotensin I to angiotensin II, as it was demonstrated in a hamster sponge model [32]. Intraperitoneal injection of the de-granulating compound 48/80 causes a vigorous angiogenic response in vivo [36, 37].

An increased number of mast cells have been demonstrated in angiogenesis associated with vascular tumors, such as hemangioma and hemangioblastoma, as well as a number of hematological and solid tumors, including lymphomas, multiple myeloma, myelodysplastic syndrome, B-cell chronic lymphocytic leukemia, breast cancer, colorectal cancer, uterine cervix cancer, melanoma, and pulmonary adenocarcinoma, in which mast cell accumulation correlate with increased neovascularization, mast cell VEGF and FGF-2 expression, tumor aggressiveness and poor prognosis [38].

Cross-talk between NK cells and mast cells

In common with MCs, NK cell development require stem cell factor (SCF) [39]. A specific correlation between NK cell function and total serum IgE levels had been observed [40]. Moreover, NK cells produce several cytokines and chemokines related to an allergic reaction upon IgE stimulation, and exhibited cytotoxicity against IgE-coated target cells in an FcYRIII-dependent manner [41].

Uterine NK cells and MCs are of crucial importance for spiral artery remodeling and placentation. In fact, mice deficient for both NKs and MCs show markedly impaired spiral artery remodeling and their fetuses are growth-retarded. In contrast, the absence of either NKs or MCs results in only minor impairment [42].

MCs can induce NK cell accumulation in different disease models. For instance, immune surveillance by MCs is important for NK cell recruitment and viral clearance during dengue infection [43]. Human cord blood-derived MCs stimulated with virus-associated TLR3 agonist can recruit human NK via the CXCL8 and CXCR1 axis, underlining MC role as sentinel cell during early viral infections [44]. Reovirus-infected human MCs induced a sevenfold increase in recruitment and activated murine NK cells in comparison to uninfected mast cells in a subcutaneous Matrigel model. Soluble products of reovirus-infected MCs included IL-10, type I and type III IFNs [45].

Lipopolysaccharide (LPS)-activated bone marrow MCs (BMMCs) induce cell contact-dependent IFN-γ secretion by NK cells, without affecting cell-mediated cytotoxicity. Cellular interaction is partly mediated by OX40L expression on MCs [46]. In addition to LPS, stimulation of MCs

Table 1 Angiogenic factors released by mast cells and NK cells

Mast cells
FGF-2
VEGF
IL-8
TNF-α
TGF-β
NGF
Chymase
Tryptase
NK cells
VEGF
PlGF
IL-8
IL-10
TGF-β
Ang-1
Ang-2

via TLR3 and TLR9, but not with IgE/antigen, amplifies IFN-γ secretion by NK cells [46]. In a model of hepatocarcinoma, MC pro-tumoral role is associated with reduction of NK cell number and activation. In the tumor microenvironment, SCF-activated MCs release adenosine that inhibit production of IFN-γ by NK cells [47]. Enhanced CCL3-mediated recruitment of NK cells is instead observed in a orthotopic melanoma model in which TLR2-activated MCs exert anticancer properties by secreting large amounts of this chemokine [48].

NK cells and mast cells might cooperate in tumor angiogenesis

Angiogenesis is associated with pathological conditions, including chronic inflammation, fibrosis, and tumor growth. When the environment in the tissue becomes hypoxic, different inflammatory cells are recruited, including monocytes/macrophages, neutrophils, T, B and NK cells, and mast cells. All these cells are able to release a plethora of angiogenic molecules, which promote and amplify the angiogenic response.

NK cells and MCs are immune cells well-known for their role in tumor growth and angiogenesis (Table 1). It has been established that these cells synergize in different pathological conditions. In this context, it might be possible that they cooperate in the establishment of the angiogenic response occurring during tumor growth and progression. This speculative consideration could be considered a suggestion to further investigate around this potential interaction between NK cells and MCs in the control of tumor angiogenesis.

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